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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/405,920 09/24/99 CARILLO

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EXAMINER

LEE, G

ART UNIT	PAPER NUMBER
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1632

DATE MAILED:

06/30/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/405,920	Applicant(s) Carillo et al.
Examiner Gai (Jennifer) Mi Lee	Group Art Unit 1632



Responsive to communication(s) filed on _____

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 835 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

Claim(s) 18-29 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 18-29 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Applicant's cancellation of claims 1-17 without prejudice in Paper No. 2 is acknowledged. Applicant's addition of claims 18-29 in Paper No. 2 is also acknowledged. Claims 18-29 are now pending in the instant application.

Specification

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 21, 22, and 24-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register at Volume 64, Number 244, pp. 71440-71442 (also available at www.uspto.gov).

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Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

While the specification contemplates using all or part of calpastatin or any inhibitor of calpain as a method of regulating cellular levels of p53 for cancer treatment by administration of viral vectors in gene therapy comprising the nucleic acid encoding calpastatin, the specification fails to describe all or part of calpastatin or any other calpain inhibitors and its function in regulating cellular levels of p53 in the specification with particularity to indicate that applicants had possession of the claimed invention to any and all variants of calpastatin or any other calpain inhibitors. Page 5 of the specification discloses several inhibitory compounds which can be used within the framework of the instant invention such as protease inhibitors, calcium chelators or calpastatin or any fragment or derivative thereof. The specification, page 6, only discloses that various fragments or derivatives of calpastatin can be used within the framework of the present invention and that any molecule obtained from SEQ ID NO: 1 and 2 via modifications by any mutation, deletion, substitution, addition and/or modification of one or more nucleotides. The specification on page 6, further states that the modification may be carried out with various ends depending on the vector. The claimed invention as a whole is not adequately described if the

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claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case the claimed embodiments of all or part of calpastatin as a method for regulating cellular levels of p53 by the administration of viral vectors encoding all or part of calpastatin in gene therapy, lack a written description. The specification fails to describe the structure of all or part of calpastatin and it was unknown as of applicants effective filing date that any and all fragments of calpastatin would have the properties of regulating cellular levels of p53. The skilled artisan cannot envision the detailed chemical structure of all or part of calpastatin from the instant disclosure and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Therefore, only the full length SEQ ID NO: 1 and 2 of human calpastatin meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-*

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Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Enablement

Claims 18-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and method of regulating cellular levels of p53 protein comprising direct intra-tumoral administration of a vector comprising a nucleic acid encoding a full length calpastatin wherein the calpastatin inhibits the activity of calpain upon its expression in the cells, does not reasonably provide enablement for a method of regulating cellular levels of p53 protein comprising any and all methods of administering to any and all cells a vector comprising any and all nucleic acid sequences encoding a protein or polypeptide which inhibits the activity of calpain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 18-25 and 29 are drawn to a method of regulating cellular levels of p53 protein comprising administrating to cells a vector comprising a nucleic acid encoding a protein or polypeptide wherein the protein or polypeptide is an inhibitor of the activity of calpain.

Applicant's claim to a method of administering a nucleic acid sequence encoding calpastatin in a viral delivery vector for regulating cellular levels of p53 protein encompasses a therapeutic use for cancer therapy (claims drawn to regulating cellular levels of p53 alone does not necessarily provide a use consistent with specification on page 1 as a new method for the

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treatment of cancer) and is not enabling for any and all methods of administering to any and all cells a viral vector comprising any and all nucleic acid sequences encoding a protein or polypeptide which inhibits the activity of calpain that is encompassed in the breadth of the claimed invention. In the Examples, the specification teaches only an *in vitro* assay of calpastatin or other protease inhibitors interaction on the cellular levels of p53 wherein the calpain inhibitors are capable of inhibiting the degradation of p53 (pages 19-22). In another example, the specification teaches the construction of the recombinant adenovirus vector containing the sequence encoding calpastatin under the control of the RSV-LTR promoter (page 24).

With regards to mice models for treating cancer, the importance of relevant animal models for support of enablement is imperative in the determination of effectiveness of treatment or effect of vectors in gene therapy. With regards to extrapolating from *in vitro* data of the specification to gene therapy of cancer, the importance of relevant animal models for support of enablement is imperative in the determination for effectiveness of gene therapy. This observation is supported by Orkin et al. in the “Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy” (see pages 10-11 and 14). On page 11, second and third paragraphs, Orkin et al emphasize the importance of relevant animal models, and state that many “mouse models often do not faithfully mimic the relevant human conditions.” Orkin et al also indicated that when dealing with cancer, the relevance of animal models appears to be less predictive than with other single-gene disorders. Note that the

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expression levels have not been demonstrated with regard to rendering treatment to a model for cancer.

While the claimed invention is directed to any and all nucleic acid encoding a protein or polypeptide which inhibits the activity of calpain, the claims also encompass any and all route of administration comprising the therapeutic gene i.e. calpastatin to regulate the cellular levels of p53 protein. Furthermore, the effect of any and all nucleic acid encoding a protein or polypeptide which inhibits the activity of calpain by any and all route of administration as therapy for cancer is unpredictable in the art. Bischoff et al disclosed the limitations of intratumorally delivery in Science, Vol. 274: 373 (1996). Bischoff et al teach that the ability of the virus to spread to distant sites and to infect metastatic tumor cells needs to be addressed because direct intratumoral injection limits the potential benefit of this approach to accessible tumors (primary brain tumors and cancers of the head and neck, for example). Dachs et al (1997) further state that advances in gene therapy have been made using viral and nonviral methods, but effective and selective delivery of DNA to tumor cells remains a complex task due to a poor and disorganized blood supply, and high interstitial fluid pressure of a solid tumor (p 314, col. 1, parag. 2). As for targeting, Applicant's specification fails to provide guidance to the skilled artisan on the parameters for gene delivery (targeting) for the breadth of the claimed invention. Eck & Wilson (The Pharmacological Basis of Therapeutics, 1996) teach numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the

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tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed

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invention resolution to vector targeting had not been achieved in the art (see entire article).

Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the “search for such [useful] combinations is a case of trial and error for a given cell type” (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that “among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated” (page 409). The specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any other mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. Instead, the specification only teaches a recombinant adenoviral vector construct containing a nucleic acid encoding calpastatin polypeptide as an indicator or potential use to regulate cellular p53 levels as a method of treating cancer.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art and effective treatment for cancer therapy. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment

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of a specific disease (i.e., cancer) providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. As the claims are not limited to any specific embodiment of gene therapy nor shown direct correlative effect to regulating cellular levels of p53, despite the *in vitro* demonstration of calpains' effect on p53 degradation from the Examples in the specification. The breadth of the claims is drawn to any and all methods of administering to any and all cells a viral vector comprising any and all nucleic acid encoding a protein or polypeptide which inhibits the activity of calpain as a regulator of cellular levels of p53 protein for cancer in gene therapy, the specification fails to teach the demonstration of calpastatin correlation to regulating cellular levels of p53 protein. However, it appears from these teachings, that several parameters of the claimed invention are critical to achieving such treatment, particularly, route of delivery, parameters such as specific dosages of adenovirus, specific dosages of nucleic acid necessary for a therapeutic effect, targeting of gene transfer to specific cells (selectivity of gene transfer), promoters to regulation gene expression need to be addressed. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of cancer by any and all methods of administering to any and all cells a viral vector comprising any and all nucleic acid encoding a protein or polypeptide

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which inhibits the activity of calpain as a regulator of cellular levels of p53 protein for cancer in gene therapy, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to achieving regulatory effect of cellular p53 levels without addressing targeting, construct for delivery, route of administration, gene expression, dosage for therapeutic effect of the instant invention, in particular in the absence of a clinically relevant animal for gene therapy, and the breadth of the claims directed to the use of enormous number of gene and any gene therapy delivery construct, it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-28 are vague and indefinite for its recitation of “the activity of calpain” because the specification does not define those factors which would make the activity of calpain inhibitory or not inhibitory. The metes and bounds of the claim can not be determined.

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The term "regulating" in claim 18 is a relative term which renders the claim indefinite.

The term "regulating" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Asada et al (1989) J.

Enzym. Inhib., Vol. 3 (1): 49-56.

Claim 29 is drawn to a composition comprising a nucleic acid encoding all or part of calpastatin that has the capacity to inhibit, at least in part, calpain.

Asada et al teach a cDNA of human calpastatin as an inhibitor protein specific for calpain (page 52). Thus, Asada et al clearly anticipate claim 29 of the instant invention.

Note, the intended use of the claimed product (claim 29) must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use

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must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 26-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Nixon et al (U.S. Patent #5,629,165).

Claims 26-29 are drawn to a viral vectors or composition comprising a nucleic acid encoding a protein or polypeptide, wherein the protein or polypeptide is an inhibitor of calpain.

Nixon et al teach a viral vector, such as adenovirus, comprising a cDNA sequence encoding a calpastatin protein (column 13). Thus, Nixon et al clearly anticipate claims 26-19 of the instant invention.

Conclusion

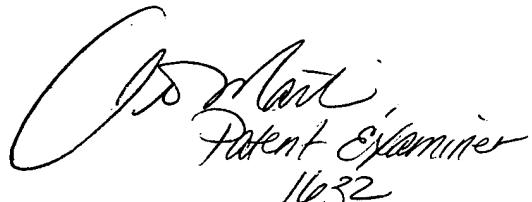
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600



A handwritten signature in black ink. The signature reads "Gai (Jennifer) Lee" on the top line, "Patent Examiner" on the middle line, and "1600" on the bottom line.